

Amendment to the Claims: Please withdraw claim 3-49 from consideration, amend claims 1 and 2 and add new claims 50-60 as follows:

Listing of the Claims: This listing replaces all previous listings.

1 (Currently amended). An isolated polypeptide comprising ~~42 or more contiguous amino acids from an~~ the amino acid sequence set forth in SEQ ID NO: 4 ~~selected from SEQ ID NOs: 2 and 12.~~

2 (Currently amended). A fusion polypeptide comprising the polypeptide of claim 1 fused to another polypeptide ~~An isolated polypeptide comprising an amino acid sequence selected from SEQ ID NOs: 2, 4 and 12.~~

3 (Withdrawn). An isolated polynucleotide encoding a polypeptide of claim 1.

4 (Withdrawn). An isolated polynucleotide comprising a nucleotide sequence selected from SEQ ID NOs: 1, 3 and 11.

5 (Withdrawn). A recombinant vector comprising the polynucleotide of claim 3.

6 (Withdrawn). A host cell comprising the vector of claim 5.

7 (Withdrawn). An isolated antibody which specifically binds to a polypeptide comprising 42 or more contiguous amino acids from an amino acid sequence selected from SEQ ID NOs: 2 and 12 or to an isolated polypeptide comprising an amino acid of SEQ ID NO: 4.

8 (Withdrawn). An isolated antibody which specifically binds to a polypeptide comprising an amino acid sequence selected from SEQ ID NOs: 39-42.

9 (Withdrawn). A method for making a polypeptide comprising culturing a host cell of claim 6 under conditions in which the polynucleotide is expressed.

10 (Withdrawn). The method of claim 9 wherein the polypeptide is isolated from the culture.

11 (Withdrawn). A method for identifying an antagonist of NPC1L1 comprising:

(a) contacting a host cell expressing a polypeptide comprising an amino acid sequence selected from SEQ ID NOs: 2, 4 and 12 or a functional fragment thereof on a cell surface, in the presence of a known amount of detectably labeled ezetimibe, with a sample to be tested for the presence of the antagonist; and

(b) measuring the amount of detectably labeled ezetimibe specifically bound, directly or indirectly, to the polypeptide;

wherein an NPC1L1 antagonist in the sample is identified by measuring substantially reduced direct or indirect binding of the detectably labeled ezetimibe to the polypeptide,

compared to what would be measured in the absence of such an antagonist.

12 (Withdrawn). A method for identifying an antagonist of NPC1L1 comprising:

(a) placing, in an aqueous suspension, a plurality of support particles, impregnated with a fluorescer, to which a host cell expressing a polypeptide comprising an amino acid sequence selected from SEQ ID NOs: 2, 4 and 12 or a functional fragment thereof on a cell surface are attached;

(b) adding, to the suspension, radiolabeled ezetimibe and a sample to be tested for the presence of the antagonist, wherein the radiolabel emits radiation energy capable of activating the fluorescer upon direct or indirect binding of the ezetimibe to the polypeptide to produce light energy, whereas radiolabeled ezetimibe that does not directly or indirectly bind to the polypeptide is, generally, too far removed from the support particles to enable the radioactive energy to activate the fluorescer; and

(c) measuring the light energy emitted by the fluorescer in the suspension;

wherein an NPC1L1 antagonist in the sample is identified by measuring substantially reduced light energy emission, compared to what would be measured in the absence of such an antagonist.

13 (Withdrawn). The method of claim 12 wherein the fluorescer is selected from yttrium silicate, yttrium oxide, diphenyloxazole and polyvinyltoluene.

14 (Withdrawn). A method of claim 11 wherein the ezetimibe is labeled with a radiolabel selected from ^3H and ^{125}I .

15 (Withdrawn). A method of claim 12 wherein the ezetimibe is labeled with a radiolabel selected from ^3H and ^{125}I .

16 (Withdrawn). A method for identifying an antagonist of NPC1L1 comprising:

(a) contacting a host cell expressing a polypeptide comprising an amino acid sequence selected from SEQ ID NOs: 2, 4 and 12 or a functional fragment thereof on a cell surface with a detectably labeled sterol or 5α -stanol and with a sample to be tested for the presence of the antagonist; and

(b) measuring the amount of detectably labeled sterol or 5α -stanol in the cell;

wherein an NPC1L1 antagonist in the sample is identified by measuring substantially reduced detectably labeled sterol or 5α -stanol within the host cell, compared to what would be measured in the absence of such an antagonist.

17 (Withdrawn). The method of claim 16 wherein the sterol or 5α -stanol is detectably labeled with a radiolabel selected from ^3H , ^{14}C and ^{125}I .

18 (Withdrawn). The method of claim 16 wherein the sterol is cholesterol.

19 (Withdrawn). A method according to claim 11 wherein the host cell is selected from a chinese hamster ovary (CHO) cell, a J774 cell, a macrophage cell and a Caco2 cell.

20 (Withdrawn). A method according to claim 12 wherein the host cell is selected from a chinese hamster ovary (CHO) cell, a J774 cell, a macrophage cell and a Caco2 cell.

21 (Withdrawn). A method according to claim 16 wherein the host cell is selected from a chinese hamster ovary (CHO) cell, a J774 cell, a macrophage cell and a Caco2 cell.

22 (Withdrawn). A mutant transgenic mouse comprising a homozygous mutation of endogenous, chromosomal NPC1L1 wherein the mouse does not produce any functional NPC1L1 protein.

23 (Withdrawn). The mouse of claim 22 wherein the mouse exhibits a reduced serum sterol or 5 α -stanol level, a reduced liver sterol or 5 α -stanol level or a reduced level of intestinal absorption of sterol or 5 α -stanol.

24 (Withdrawn). The mouse of claim 22 wherein the region of endogenous, chromosomal NPC1L1 deleted corresponds to nucleotides 790-998 of the nucleotide sequence set forth in SEQ ID NO: 45.

25 (Withdrawn). An offspring or progeny of the mouse of claim 22 wherein the offspring or progeny has inherited a mutated NPC1L1 allele of said mouse.

26 (Withdrawn). A method for screening a sample for an intestinal sterol or 5 α -stanol absorption antagonist comprising:

(a) feeding a sterol or 5 α -stanol-containing substance to a first and second mouse comprising a functional NPC1L1 gene and to a third, mutant mouse of claim 21;

(b) administering the sample to the first mouse but not the second mouse;

(c) measuring the amount of sterol or 5 α -stanol absorption in the intestine of said first, second and third mouse; and

(d) comparing the levels of intestinal sterol or 5 α -stanol absorption in said first, second and third mouse;

wherein the sample is determined to contain the intestinal sterol or 5 α -stanol absorption antagonist when the level of intestinal sterol or 5 α -stanol absorption in the first mouse and third mouse are less than the amount of intestinal sterol or 5 α -stanol absorption in the second mouse.

27 (Withdrawn). The method of claim 26 wherein the sterol is cholesterol.

28 (Withdrawn). The method of claim 27 wherein the cholesterol is radiolabeled.

29 (Withdrawn). The method of claim 26 wherein the level of sterol or 5 α -stanol cholesterol absorption is determined by measuring the level of serum sterol or 5 α -stanol in the mice.

30 (Withdrawn). A method for inhibiting NPC1L1 mediated sterol or 5 α -stanol uptake, in a subject, by administering,

to the subject, a substance identified by the method of claim 11.

31 (Withdrawn). A method for inhibiting NPC1L1 mediated sterol or 5 α -stanol uptake, in a subject, by administering, to the subject, a substance identified by the method of claim 12.

32 (Withdrawn). A method for inhibiting NPC1L1 mediated sterol or 5 α -stanol uptake, in a subject, by administering, to the subject, a substance identified by the method of claim 16.

33 (Withdrawn). A method for inhibiting NPC1L1 mediated sterol or 5 α -stanol uptake, in a subject, by administering, to the subject, a substance identified by the method of claim 26.

34 (Withdrawn). A kit comprising:

- (a) ezetimibe in a pharmaceutical dosage form; and
- (b) information indicating that NPC1L1 is a target of ezetimibe.

35 (Withdrawn). The kit of claim 34 wherein the dosage form is a tablet comprising 10 mg ezetimibe.

36 (Withdrawn). The kit of claim 34 further comprising simvastatin in a pharmaceutical dosage form.

37 (Withdrawn). The kit of claim 36 wherein the simvastatin in pharmaceutical dosage form comprises 5 mg, 10 mg, 20 mg, 40 mg or 80mg simvastatin.

38 (Withdrawn). The kit of claim 36 wherein the simvastatin in pharmaceutical dosage form and the ezetimibe in pharmaceutical dosage form are associated in a single pill or tablet.

39 (Withdrawn). A method for decreasing the level of intestinal sterol or 5 α -stanol absorption in a subject comprising reducing the level of expression of NPC1L1 in the subject.

40 (Withdrawn). The method of claim 39 wherein the subject is a mouse, rat or human.

41 (Withdrawn). The method of claim 39 wherein the level of expression of NPC1L1 in the subject is reduced by mutating NPC1L1 in the subject.

42 (Withdrawn). The method of claim 39 wherein the sterol is cholesterol.

43 (Withdrawn). A method for identifying an antagonist of NPC1L1 comprising:

(a) contacting a host cell expressing a polypeptide comprising an amino acid sequence selected from SEQ ID NOs: 2, 4 and 12 or a functional fragment thereof on a cell surface, in the presence of a known amount of a detectably

labeled substituted azetidinone, with a sample to be tested for the presence of the antagonist; and

(b) measuring the amount of detectably labeled substituted azetidinone specifically bound, directly or indirectly, to the polypeptide;

wherein an NPC1L1 antagonist in the sample is identified by measuring substantially reduced direct or indirect binding of the detectably labeled substituted azetidinone to the polypeptide, compared to what would be measured in the absence of such an antagonist.

44 (Withdrawn). A kit comprising:

(a) a substituted azetidinone in a pharmaceutical dosage form; and

(b) information indicating that NPC1L1 is a target of the substituted azetidinone.

45 (Withdrawn). An isolated mammalian cell which lacks a gene which encodes a functional NPC1L1 protein.

46 (Withdrawn). The cell of claim 45 isolated from a mutant mouse comprising a homozygous mutation of endogenous, chromosomal NPC1L1 wherein the mouse does not produce any functional NPC1L1 protein.

47 (Withdrawn). The cell of claim 46 wherein the mutation is of a gene encoding an amino acid sequence of SEQ ID NO: 12.

48 (Withdrawn). The cell of claim 45 isolated from the duodenum, gall bladder, liver, small intestine or stomach tissue.

49 (Withdrawn). The cell of claim 48 which is an enterocyte.

50 (New). A polypeptide of claim 2 comprising a polypeptide selected from the group consisting of a glutathione-S-transferase (GST) tag polypeptide, a hexahistidine tag polypeptide, a maltose binding protein tag, a haemagglutinin polypeptide tag, a cellulose binding protein tag and a myc tag polypeptide.

51 (New). A polypeptide of claim 1 which is labeled with a member selected from the group consisting of ^{32}P , ^{35}S , ^3H , $^{99\text{m}}\text{Tc}$, ^{123}I , ^{111}In , ^{68}Ga , ^{18}F , ^{125}I , ^{131}I , $^{113\text{m}}\text{In}$, ^{76}Br , ^{67}Ga , $^{99\text{m}}\text{Tc}$, ^{123}I , ^{111}In and ^{68}Ga .

52 (New). A polypeptide of claim 1 which is bound to cholesterol.

53 (New). A polypeptide of claim 52 wherein said cholesterol is radiolabeled.

54 (New). A polypeptide of claim 53 wherein the radiolabel is ^{125}I or ^3H .

55 (New). A polypeptide of claim 1 which is bound to ezetimibe.

56 (New). A polypeptide of claim 55 wherein said ezetimibe is radiolabeled

57 (New). A polypeptide of claim 56 wherein the radiolabel is ^{125}I or ^3H .

58 (New). A polypeptide of claim 55 wherein the ezetimibe is BODIPY labeled ezetimibe.

59 (New). A polypeptide of claim 1 complexed with an antibody which binds specifically to said polypeptide.

60 (New). A polypeptide of claim 1 which is glycosylated.